**REMARKS**

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on March 2, 2010. Claims 1-58 and 67-77 had been pending, claims 59-66 having been previously cancelled without prejudice or disclaimer. Claims 2, 4-13, 15-58, 69, 71-77 were withdrawn, and claims 1, 3, 14, 67, 68, and 70 were examined. Pending entry of this amendment, claims 1, 3, and 14 have been amended, claims 67, 68, and 70 have been canceled without prejudice or disclaimer, and claims 78, 79, and 80 have been added. Thus, with this amendment, claims 1, 3, 14, and 78-80 are pending and under consideration.

Claims 1, 3, and 14 have been amended. Claim 1 has been amended to recite:

> (i) contacting *in vitro* cells comprising a G protein-coupled receptor protein comprising substantially the same amino acid sequence represented by SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 8, wherein the G protein-coupled receptor protein has a G protein-coupled receptor function, with a fatty acid or a salt thereof in the presence of the compound or its salt and in the absence of the compound or its salt,
>
> (ii) assaying a cell-stimulating activity stimulated by binding of the fatty acid or a salt thereof to the G protein-coupled receptor protein in the presence of the compound or its salt and in the absence of the compound or its salt, and
>
> (iii) comparing the cell stimulating activity stimulated by binding of the fatty acid or a salt thereof to the G protein-coupled receptor protein in the presence of the compound or its salt and in the absence of the compound or its salt, wherein a change in cell-stimulating activity indicates that the compound or its salt changes a binding property of the G protein-coupled receptor protein.

Support for that amendment is found in the specification, for example, at least at page 77, lines 11-17 and original claim 1.

Claim 3 has been amended to recite:

> i) contacting *in vitro* a G protein-coupled receptor protein comprising substantially the same amino acid sequence represented by SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 8,

> wherein the G protein-coupled receptor protein has a G protein-coupled receptor function, with a fatty acid or a salt thereof in the presence of the compound or its salt and in the absence of the compound or its salt,
>
> ii) assaying the binding of the fatty acid or a salt thereof to the G protein-coupled receptor protein in the presence of the compound or its salt and in the absence of the compound or its salt, and
>
> iii) comparing the binding of the fatty acid or a salt thereof to the G protein-coupled receptor protein in the presence of the compound or its salt and in the absence of the compound or its salt, wherein a change in binding indicates that the compound or its salt changes a binding property of the G protein coupled receptor protein.

Support for that amendment is found at page 77, lines 11-17 and in original claim 1.

Claim 14 has been amended simply to clarify the claim language and promote consistency with its parent claim 1. That amendment is supported by the specification, for example, at least at page 77, lines 18-28 and original claim 14.

Applicants have added claims 78, 79, and 80, which depends from claims 1, 3, and 14, respectively. Claims 78, 79, and 80 indicate that "the compound is an agonist or antagonist to a G protein-coupled receptor protein." Support is found in the specification, for example, at least at original claim 3.

As all of these are reasonably conveyed by the original claims and the specification, no new matter has been added. Applicants respectfully request entry of these claims.

**Specification**

The title of the application is rejected as allegedly being "not descriptive." Action at page 2. Applicants have amended the title to "NOVEL SCREENING METHOD USING A G PROTEIN COUPLED RECEPTOR THAT BINDS A FATTY ACID."

In addition, the Office requires an updated priority statement which includes the national phase filing information for this application. *Id.* Applicants respectfully point out that the

Preliminary Amendment filed July 15, 2005, included an amendment to the specification to update the priority information. Applicants note, however, that the amendment was not properly coded on PAIR. Applicants include herewith an amendment to the Specification in order to clarify and update the priority statement.

**Rejections of claims 1, 3, 14, 67, 68, and 70 under 35 U.S.C. § 112, 2nd paragraph**

Alleged Omission of Essential Steps

Claims 1, 3, 14, 67-68, and 70 are rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly being incomplete for "omitting essential steps." Action at page 3. Specifically, the Office states that the omitted steps include "method steps that indicate how the receptor protein and the fatty acid are used to screen a compound that changes the binding property of the receptor and the fatty acid." *Id.* The Office further states that "the method steps fail to recite a step where the compound to be screened is used in the method." *Id.*

Applicants respectfully traverse. Nonetheless, solely to facilitate prosecution and not in acquiescence to the Office's rejection, Applicants have amended the claims to recite additional steps. For example, claim 1 recites the following steps:

> (i) contacting *in vitro* cells comprising a G protein-coupled receptor protein. . . in the presence of the compound or its salt and in the absence of the compound or its salt . . .
>
> (ii) assaying a cell-stimulating activity . . .
>
> (iii) comparing the cell-stimulating activity . . . .

Likewise, claim 3 recites the following steps:

> (i) contacting *in vitro* cells comprising a G protein-coupled receptor protein. . . in the presence of the compound or its salt and in the absence of the compound or its salt . . .
>
> (ii) assaying the binding of the fatty acid or a salt thereof to the G protein-coupled receptor protein. . .

> (iii) comparing the binding of the fatty acid or salt thereof to the G protein-coupled reeeptor protein . . . .

Independent claims 1 and 3 and dependent claims 14 and 78-80, therefore, indicate how the G protein-coupled receptor protein and fatty acid are used to screen the compound. As noted above, claims 67, 68, and 70 have been canceled without prejudice or disclaimer, thus rendering the rejection moot with respect to those claims. Accordingly, Applicants respectfully request withdrawal of the rejection.

Alleged Indefiniteness

Claims 1, 3, 14, 67-68, and 70 are also rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly "being indefinitely for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Action at page 3. Specifically, the Office alleges that claim 1 is indefinite "because it is unclear what a 'salt' of a receptor is." *Id.* The Office alleges that the specification "uses this term but does not explain what is meant by it or structurally define a 'salt' of a receptor." *Id.*

The Office also rejects claims 67, 68, and 70 as indefinite because the elements recited in the claims "do not constitute a proper Markush group," Action at page 4, while the Office further rejects claim 68 as indefinite "because it twice recites 'a drug for preventing/treating in line 12.'"

Applicants respectfully traverse. Applicants have deleted from the claims language relating to a salt of a receptor. Furthermore, as noted above, claims 67, 68, and 70 are canceled, thereby rendering the rejection moot with respect to those claims. Applicants respectfully request withdrawal of the rejection.

**Rejections of claims 1, 3, 14, 67-68, and 70 under 35 U.S.C. § 112, 1st paragraph, enablement**

Claims 1, 3, 14, 67-68, and 70 are rejected under 35 U.S.C. § 112, 1st paragraph, because the specification allegedly "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Action at page 5.

Method of Screening

The Office alleges that the specification does not reasonably provide enablement for "[a] method of screening as recited in claims 1, 3, or 14, or a method for confirming as recited in claims 67, 68, or 70." Action at page 5. However, the Office acknowledges that the specification is enabling for:

> A method of screening, or confirming that a drug binds to a receptor, comprising
>
> i) contacting *in vitro* a polypeptide comprising SEQ ID NO:1 with a fatty acid in the presence of a test compound and determining (a) the binding of the fatty acid to the receptor or (b) a cell-based activity stimulated by binding of the fatty to the receptor,
>
> (ii) contacting *in vitro* a polypeptide comprising SEQ ID NO:1 with a fatty acid in the absence of a test compound and determining (a) or (b), and
>
> (iii) comparing the determinations made in steps (i) and (ii), wherein a change in binding or cell-based activity in the presence of the test compound as compared to the absence of the test compound indicates that the test compound changes the binding between the fatty acid and the receptor, or changes the cell-based activity stimulated by binding of the fatty acid to the receptor.

*Id.* at 4. As noted above, the amendment to claim 1 recites the following method steps:

> (i) contacting *in vitro* cells comprising a G protein-coupled receptor protein . . . in the presence of the compound or its salt and in the absence of the compound or its salt . . .
>
> (ii) assaying a cell-stimulating activity . . .

(iii) comparing the cell-stimulating activities . . . ."

Similarly, the amendment to claim 3 recites the following method steps:

(i) contacting *in vitro* cells comprising a G protein-coupled receptor protein. . . in the presence of the compound or its salt and in the absence of the compound or its salt . . .

(ii) assaying the binding of the fatty acid or a salt thereof to the G protein-coupled receptor protein. . .

(iii) comparing the binding of the fatty acid or salt thereof to the G protein-coupled receptor protein . . . .

As claims 14 and 78-80 ultimately depend from independent claims 1 or 3, they also contain the same steps. As noted above, claims 67, 68, and 70 are canceled. Accordingly, one of skill in the art would clearly understand how to make and use the claimed invention without undue experimentation, and the pending claims are enabled. Applicants respectfully request reconsideration and withdrawal of the rejection.

Amino Acid Sequences

The Office further alleges that the specification does not provide enablement for embodiments encompassing methods of screening using "'the same or substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 1' or 'its partial peptide.'" Action at pages 6-7. According to the Office, the specification describes a large genus of mutations that can be made in SEQ ID NO:1, but does not provide any guidance as to which substitutions to make to achieve any desired property, a defined difference in structure, or a difference in function. *Id.* at 7. Moreover, the Office states that the claims "do not place any structural or functional limitations on the proteins to be used." *Id.*

Applicants respectfully traverse. First, the claims do recite a function. Specifically, the claims require that "the G protein-coupled receptor protein has a G protein-coupled receptor function." Second, the specification does provide guidance regarding the recited amino acid

sequences sufficient to enable the present claims. For example, the specification defines G protein-coupled receptors, describing both their structure and function. *See* Specification, p. 1, ll. 11-24. For example, the specification notes that GPCRs possess a "common structure containing seven transmembrane domains" and that they "transmit signals to cells via binding with physiologically active substances." In addition, the specification teaches that proteins having substantially the same amino acid sequence as the amino acid sequences represented by SEQ ID NO: 1, SEQ ID NO: 3, and SEQ ID NO: 8 preferably have an activity "substantially equivalent" to these amino acid sequences. *Id.* at p. 32, ll. 19-24. "Examples of substantially equivalent activity described above include a ligand binding activity, a signal transduction activity, etc." *Id.* at p. 32, ll. 29-31. The specification explains that such activities can be determined according to publicly known methods. *Id.* at p. 33, ll. 1-3.

In addition, the specification states that amino acids that are "the same or substantially the same" as SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:8 include sequences having at least 85%, 90%, and 95% homology to these sequences. *See* Specification, p. 32, 19-24. The specification teaches that such proteins may comprise a) deletion of at least 1 or 2 amino acids (preferably approximately 1-30 amino acids), b) addition of at least 1 or 2 amino acids (preferably approximately 1 to 30 amino acids), c) substitution of at least 1 or 2 amino acids (preferably approximately 1-30 amino acids), or d) combinations of all of these. *Id.* at p. 33, ll. 4-16. The specification also teaches how to determine homology of amino acid sequences using the BLAST algorithm, and provides parameters for using the algorithm. *Id.* at p. 32, ll. 25-28.

Accordingly, contrary to the Office's conclusion, the specification does provide sufficient guidance on substitutions that can be made to achieve a desired property and also defines the structure and function of the GPCR variants. Indeed, the specification demonstrates that the

variants would be GPCRs, and it defines the structure of these receptors. Thus, the specification demonstrates that the variants would have the same structure. Moreover, the specification describes the function of GPCRs and provides support for functional limitations of the recited variants, noting that the variants have a substantially equivalent activity to the GPCRs having the recited sequences.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

Alleged Transgenic Animal

The Office also alleges that the claims encompass methods of screening using transgenic animals. Specifically, the Office references claim 14 as reciting "use of 'cells containing a G protein-coupled receptor protein comprising . . . SEQ ID NO:1" as evidence that claim 14 encompasses a method of screening transgenic animals. Action at page 8.

Claim 14 depends from claim 1, which recites a screening method comprising contacting cells *in vitro*. Accordingly, the claim does not require a transgenic animal, and Applicants respectfully request withdrawal of the rejection.

Method of Confirming

Finally, while acknowledging that the specification "enables the skilled artisan to use the claimed method to identify modulators of the interaction between fatty acids and the protein of SEQ ID NO:1," the Office alleges that "the specification does not enable the skilled artisan to use the claimed method 'for confirming' 'a drug for preventing/treating diabetes mellitus' as recited in claims 67, 68 and 70." Action at page 9. As claims 67, 68, and 70 are canceled, this rejection is moot, and Applicants respectfully request withdrawal of the rejection.

**Rejections of claims 1, 3, 14, 67-68, and 70 under 35 U.S.C. § 112, 1st paragraph, written description**

Claims 1, 3, 14, 67-68, and 70 are rejected under 35 U.S.C. § 112, 1st paragraph, for allegedly "failing to comply with the written description requirement." Action at page 10. Referring to the prior enablement rejection, the Office states that the genus of polypeptides encompassed by the claims is "highly variant because a significant number of structural differences between genus members are permitted." The Office further states that the claims "do not require that polypeptides possess any particular conserved structure or function, or other disclosed distinguishing feature." *Id.* The Office further alleges that the specification "fails to describe or teach any other polypeptide which differs from SEQ ID NO:1 and that retains the characteristics of the parent polypeptides." *Id.* However, the Office acknowledges that written description may be satisfied through disclosure of relevant identifying characteristics, such as "functional characteristics coupled with a known or disclosed correlation between structure and function." *Id.*

Applicants respectfully traverse. As discussed above in the enablement section, the claims have been amended to indicate that "the G protein-coupled receptor protein has a G protein-coupled receptor function." As noted there, the specification discusses amino acid substitutions that may be made to the recited sequences and notes that variants preferably have an activity "substantially equivalent" to the recited amino acid sequences. Examples of such activity include ligand binding activity and signal transduction activity. Thus, the specification provides adequate written description for the present claims. Applicants respectfully request reconsideration and withdrawal of the rejection.

**Rejections of claims 1, 3, 14, 67-68, and 70 under 35 U.S.C. § 102(b)**

Claims 1, 3, 14, 67-68, and 70 are rejected under 35 U.S.C. § 102(b), for allegedly being anticipated by Sidhu et al. (J. Physiol., 528(1): 165-176 (2000)) ("Sidhu"). *Id.* at 12. At the outset, the Office states that the recitation in the preamble that the method of screening changes the binding property of a GPCR "is interpreted as an intended use and bears no accorded patentable weight to distinguish the claim over one from the prior art." Action at page 12. Thus, the Office alleges that the claims encompass "any method of screening that comprises using a [GPCR] of SEQ ID NO:1" *Id.* at 13. The Office cites Sidhu as teaching the application of dodecanoic acid (a fatty acid) to the enteroendocrine cell line STC-1, and states that the STC-1 cell line contains a GPCR that is 100% identical to SEQ ID NO:1. The Office further relies on Sidhu to teach a difference in $CA^{2+}$ response when dodecanoic acid was applied alone to STC-1 cells and when it was applied in the presence of BSA.

Applicants respectfully traverse. Sidhu does not teach each and every element of the claims. The body of independent claims 1 and 3, specifically subpart (iii), recites that a change in binding or cell stimulated activity "indicates that the compound changes a binding property of the G protein-coupled receptor." Sidhu is silent as to whether BSA changes a binding property of a G protein-coupled receptor and, consequently, cannot meet this element of the independent claims.

Moreover, Sidhu suggests that the difference in $Ca^{2+}$ response is not due to a change in the binding property of the G protein-coupled receptor. Sidhu notes that BSA is used to create a fatty acid aqueous solution in which fatty acids are soluble. Sidhu at page 173. Sidhu postulates that the differences in $Ca^{2+}$ response in the presence of BSA:

> [s]uggest that enteroendocrine cells may not be responding to the monomeric form of fatty acids. Indeed, it is conceivable that

> enteroendocrine cells may be responding to fatty acid which is not in solution at all and that it is this insoluble component which is involved in the fatty acid signal transduction pathway.

*Id.* at 174. Accordingly, Sidhu does not suggest that BSA necessarily changes a binding property of a G protein-coupled receptor. To the contrary, Sidhu suggests that the difference in $Ca^{2+}$ response is due to a low level of available fatty acid resulting from the high solubility of fatty acids in BSA. *See id.* Thus, Sidhu does not anticipate the claimed methods, as it does not show that BSA necessarily changes a binding property of the GPCR.

As claims 14 and 78 depend from claims 1 and 3, they are not anticipated for the same reasons stated above. Claims 67, 68, and 70 have been canceled, and thus the rejection is moot as to those claims. Thus, Applicants respectfully request withdrawal of the rejection.

**CONCLUSION**

For the foregoing reasons, claims 1, 3, 14, and 78-80 satisfy the requirements of 35 U.S.C. § 112, 1st and 2nd paragraphs, as well as 35 U.S.C. § 102. Applicants respectfully request the issuance of a Notice of Allowance. Please grant any further extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: August 26, 2010

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